



The role of epigenetics in allergy and asthma development

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Purpose of review

Epigenetic mechanisms are known to play a crucial role in the pathogenesis of asthma, allergic rhinitis, atopic dermatitis, food allergy, and other allergic disorders, especially through mediating the effects of the environmental factors, well recognized allergy-risk modifiers. The aim of this work was to provide a concise but comprehensive review of the recent progress in the epigenetics of allergic diseases.

Recent findings

Recent few years have substantially expanded our knowledge on the role of epigenetics in the pathogenesis and clinical picture of allergies. Specifically, it has been shown that epigenetic marks, especially DNA methylation, possess a diagnostic potential for atopic sensitization, asthma, allergic rhinitis, and food allergy. DNA methylation can be a predictor of clinical responses in controlled allergen challenges, including oral food challenges. Furthermore, direct or indirect targeting epigenetic mechanisms, this time especially histone modifications, was able to favorably affect expression of the genes underlying allergies and generally improve airway biology in allergic diseases or their animal models.

Summary

Further studies are needed to explore the diagnostic and therapeutic potential of epigenetic modifications in allergies and to develop respective clinical tools.

Keywords

allergy, asthma, DNA methylation, epigenetic, histone modification

INTRODUCTION

Asthma and other allergic diseases belong to the most common chronic inflammatory diseases, especially in children. As allergies are multifactorial diseases triggered by gene-by-environment interactions, classical genetics including large genome-wide association studies (GWASs) was unable to explain such high and still increasing prevalence of allergic disorders as well as their phenotypic heterogeneity [1,2].

A comprehensive, multifactorial list of environmental risk factors has been proposed to contribute to the development of asthma and other allergic disorders. Those include tobacco smoke, allergen exposure, viral respiratory tract infections, ozone, diesel exhaust particles, SO₂ and NO₂ pollution, and others [3,4]. On the other hand, reduction in some exposures, such as contact with farm microorganisms or traditional diets has also been found to contribute to the increased risk of asthma and allergies. The effects of those environmental influences are thought to be, at least partly, mediated by the epigenetic mechanisms, such as DNA methylation and histone modifications (Fig. 1) [5].

This review discusses our current understanding of the role of epigenetic modifications in the development of asthma and other allergic diseases. Furthermore, it highlights the potential role of epigenetics as biomarker in allergic diseases and as a promising target for novel antiallergic therapies.

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KEY POINTS

- Epigenetic mechanisms are involved in the pathogenesis of allergic disorders, among others through mediating the environmental effects.
- Epigenetic marks, especially DNA methylation, have been recently shown to demonstrate a potential for the development of diagnostic tools for allergies.
- Epigenome-modifying tools, mostly those targeting histone modifications, have been lately demonstrated to possess antiallergic therapeutic abilities.

CLASSICAL EPIGENETIC MECHANISMS

DNA methylation

DNA methylation is one of the first identified and, at the same time, one of the most widely studied epigenetic modifications in humans. It occurs by covalent methylation of a cytosine within the CpG dinucleotides. The CpG dinucleotides cluster into so-called CpG islands (CGIs) [6].

There are three canonical families of molecular factors that manage DNA methylation. First group is the DNA methyltransferases (DNMTs), the writers

that carry a methyl group and deposit it of the fifth carbon of the cytosine, thus forming a 5-methylcytosine (5mC) in the DNA backbone. The most known mammalian DNMTs are the DNMT3A and DNMT3B that create the de novo DNA methylation in the first place; once created, this covalent modification can be preserved by means of DNMT1 throughout DNA replications [7]. The methyl-CpG-binding domain (MBD) proteins, forming the second family of the enzymes, are the readers that recognize the symmetrically methylated CpGs and recruit other protein complexes. The third group contains ten-eleven translocation proteins (TET1-3), which are the erasers catalyzing the initial step of active DNA demethylation, that is, conversion of 5mC into a 5-hydroxymethylcytosine (5hmC) [8] (Fig. 2). The major role of DNA methylation in mammals is to repress gene expression by recruiting different silencing protein complexes, such as histone deacetylases (HDACs), which in turn can block the transcription machinery [9].

Histone modifications

Histone proteins are prone to various types of covalent posttranslational modifications (PTMs) including acetylation, methylation, phosphorylation,

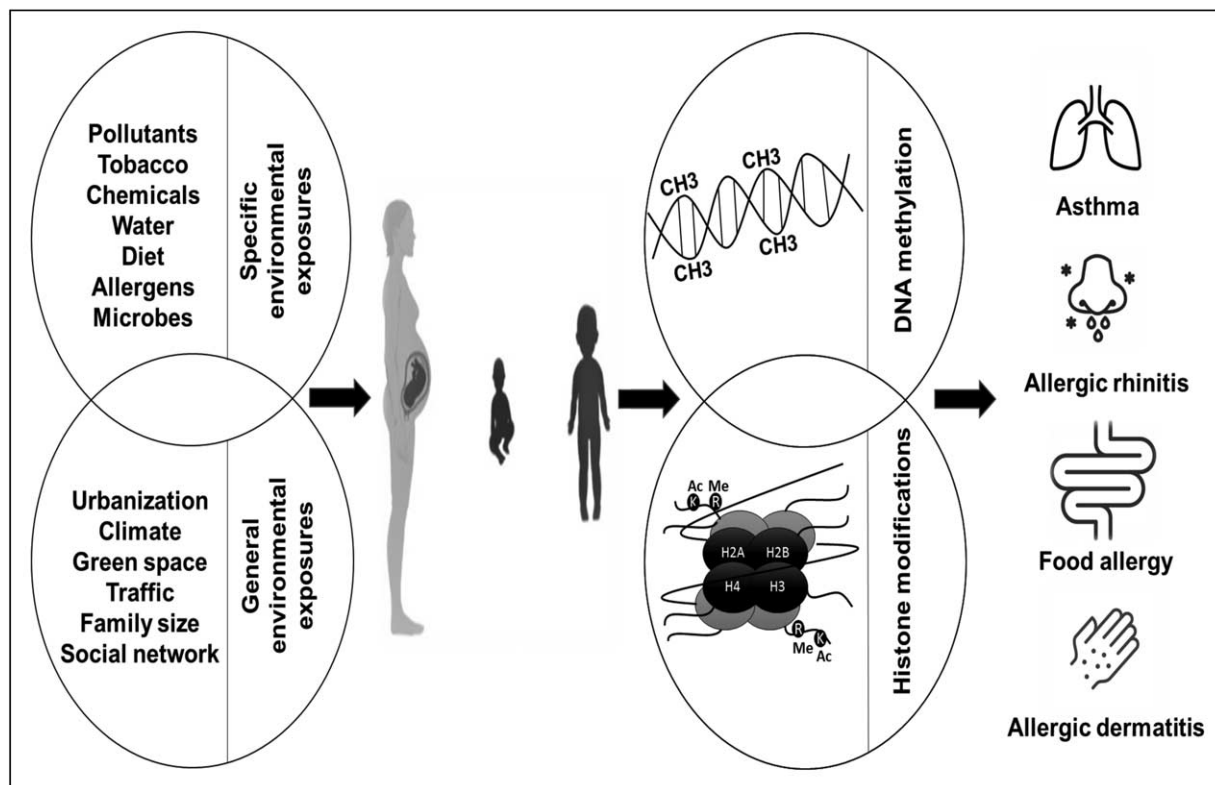


FIGURE 1. Contribution of the environmental factors to the development of allergic disorders through the epigenetic mechanisms.

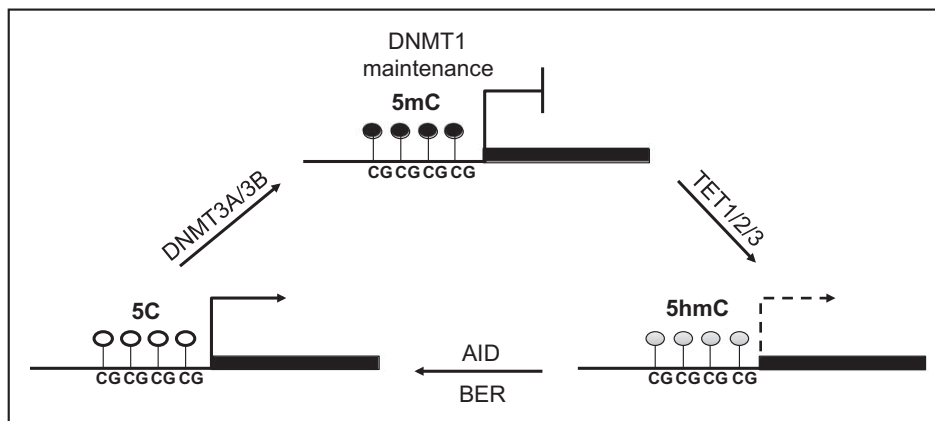


FIGURE 2. Methylation and demethylation cycle of cytosine. DNA methyltransferase enzymes (DNMT3A/3B) can catalyze de novo methylation of a cytosine (5C) in CpG dinucleotides clustered into so-called CpG islands. DNMT1 in turn maintains methylation of a cytosine. Cytosine methylation can be reverted by ten-eleven translocation proteins (TET1-3), converting a 5-methylcytosine (5mC) into a 5-hydroxymethylcytosine (5hmC), followed by activation-induced deaminase (AID) and base-excision repair (BER).

ubiquitination, and sumoylation. Histone acetylation and methylation refer to the addition of specific chemical groups to the lysine or both lysine and arginine residues of the N-terminal tail of the histone molecules, respectively. Histone methyltransferases (HMTs) and acetyltransferases (HATs) carry the respective functional groups to their histone substrates, thus catalyzing the processes of histone methylation or acetylation [5,10]. Some histone modifications can provide a solid ground for other molecules to bind to their genomic targets like in the case of histone methylation. The others, such as histone acetylation, can decrease the affinity between the histone molecules and DNA or between the adjacent nucleosomes, which can as a result dynamically de-compact the chromatin and make it accessible to a variety of functional proteins and chromatin remodeling factors. Thus, histone acetylation is in general functionally associated with gene activation [11]. Histone methylation can be in turn associated with either gene repression or activation, depending on the position of the amino acid residue within the N-terminal tail and the number of methyl groups added. Substantial efforts have been made to clarify the mechanism underlying this phenomenon, including studies on the trithorax (TrxG) and polycomb (PcG), the two complex and highly conserved protein groups. TrxG system preserves the active state of the gene through tri-methylation of H3K4 (H3K4me3), whereas the PcG complex contributes to gene repression by means of H3K27 tri-methylation (H3K27me3). Moreover, TrxG and PcG group proteins maintain a cellular memory throughout cell divisions [12] (Fig. 3).

THE ROLE OF EPIGENETICS IN ALLERGIC DISORDERS

Asthma

Despite years of efforts, asthma remains an important public health problem worldwide. Even more than that, in the global scale, there has been an increase in the prevalence of asthma in the recent decades, which seems to be related to the constantly progressing industrialization, urbanization, and westernization of the lifestyle. Indeed, considering the rather constant genetic background, impossible to change within a short time interval, this rise in the asthma prevalence seems to be related to the increased exposure to pollution of different types as well as decreased exposure to the natural environmental factors, such as farming and related micro-organisms or traditional diets [13]. Both favorable and unfavorable downstream biological effects of those environmental influences are thought to be mediated, at least partly, by the epigenetic mechanisms (Fig. 1) [14]. Most of the studies investigating the role of the epigenetic modifications in asthma have focused on DNA methylation, not only due the rather easy accessibility of the study material, which can be any DNA type already collected for other (genetic) purposes) or the fact that DNA methylation was relatively early discovered, but predominantly because of importance of this epigenetic mechanism for the regulation of gene expression [15].

Alterations of the DNA methylation status in the genes specific for different subset of T helper (CD4⁺) cells are considered as a very good example

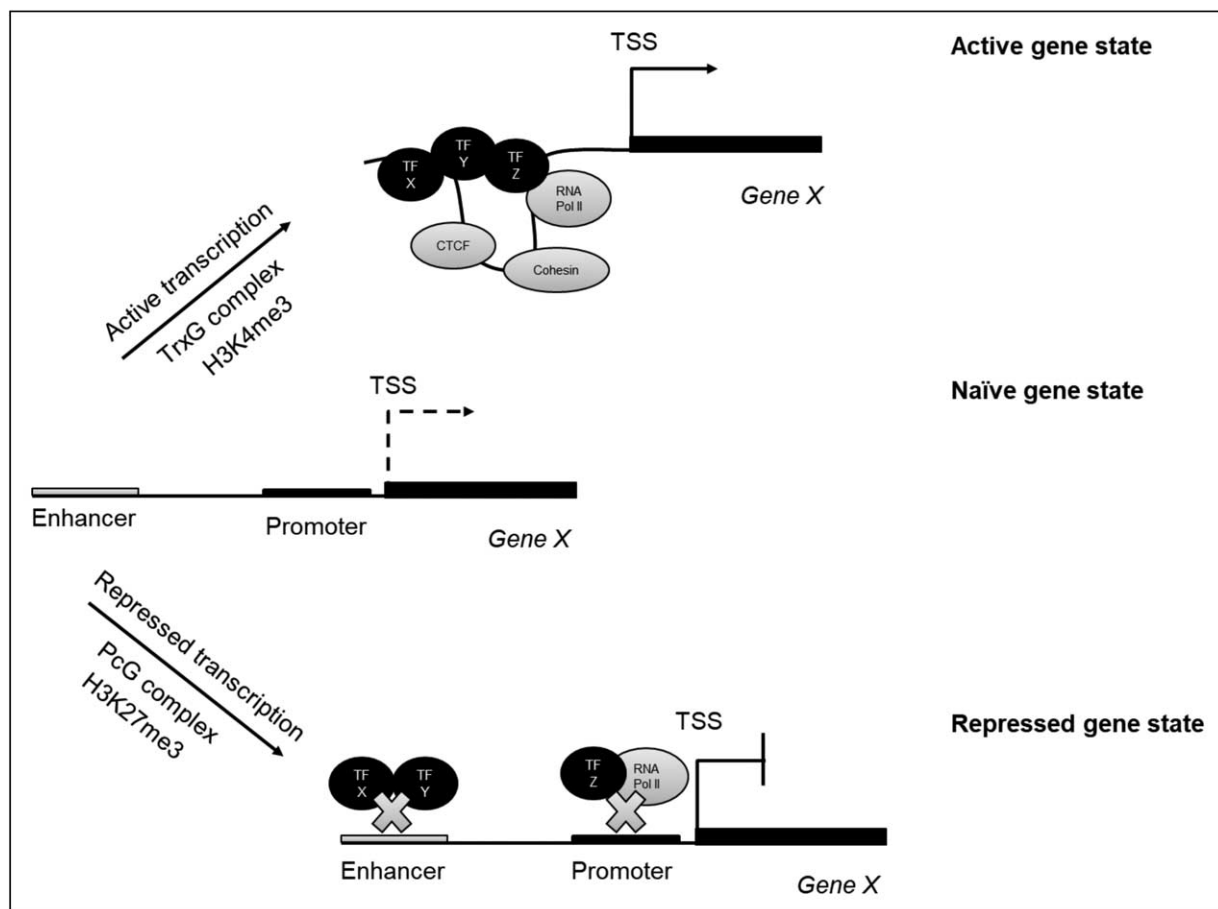


FIGURE 3. Regulation of a random gene (*Gene X*) by trithorax (TrxG) and polycomb (PcG) group proteins. Shifting the gene from the naïve into the active state by the TrxG complex is mediated by the histone mark H3K4me3 and chromatin remodeling proteins that create the transcription loop between the enhancer(s) and the promoter region. The PcG complex can in turn repress the gene activity through the histone mark H3K27me3 and remodeling proteins preventing transcription factors (TFs) from binding to their target sites. TSS, transcription start site.

of how epigenetic modulation can influence the development of asthma and allergic diseases [3]. For instance, in CD4⁺ T-cells, the allergic sensitization is capable of inducing demethylation of the interleukin 4 (*IL-4*) encoding gene (*IL4*) at its promoter region, thus contributing to the subsequent development of allergic airway inflammation. Differential methylation of the DNA at the promoter regions of *IL4* or interferon γ (*IFN- γ*) locus (*IFNG*) was observed between asthmatic patients and non-asthmatic individuals [16]. Furthermore, in children suffering from allergic asthma, and thus treated with house dust mite (HDM) allergen-specific immunotherapy, HDM sensitivity and production of IL-4, IL-5, and IL-2 by peripheral blood mononuclear cells (PBMCs) were lower, whereas DNA methylation at the promoter region of *IL4* as estimated in PBMCs was higher following the allergen challenge compared with the untreated group [17]. Naturally, the involvement of DNA methylation in the pathophysiology of asthma goes far beyond CD4⁺ hallmark

molecules. DNA methylation levels at the promoter region of *TET1* were associated with childhood asthma and traffic-related air pollution [18]. Subsequent studies performed in *TET1*-deficient mice in a model of allergic airway inflammation demonstrated that loss of *TET1* was able to increase disease severity including lung eosinophilia and airway hyperresponsiveness. Those effects were mediated by alterations of DNA methylation at loci belonging to IFN- γ and aryl hydrocarbon receptor pathways [19]. It was also demonstrated that cord blood DNA methylation status at *SMAD3*, a gene encoding SMAD family member 3, links maternal asthma with childhood asthma risk [20]. Distinct patterns of DNA methylation were reported to be associated also with abnormalities in the phenotype of the airway smooth muscle cells (ASMCs), typically observed in severe asthma patients [21].

Similarly to DNA methylation, also histone modifications contribute to the development and pathophysiology of asthma by modifying the

accessibility of genomic DNA to the transcriptional machinery [10]. Treatment with a selective H3K27me3 demethylation inhibitor GSK-J4 ameliorated allergic airway inflammation, airway hyper-responsiveness, and airway remodeling in a mouse HDM-based model. In addition, GSK-J4 was able to reduce in-vitro synthesis of contractile proteins by human ASMCs [22[¶]]. Comparative analysis of ASMCs from asthmatic patients and nonasthmatic individuals demonstrated in turn that, when compared with the latter, the former had higher H3K18 acetylation as well as higher histone acetyltransferase p300 binding levels at the *IL8* promoter. Moreover, application of a BET (bromoterminal and extraterminal) bromodomain inhibitor, blocking the histone acetylation function of BET group proteins, inhibited secretion of IL-8 from ASMCs [23].

Atopic dermatitis

Atopic dermatitis or atopic eczema is a chronic inflammatory skin disorder characterized by recurrent eczematous lesions, intense itching, high degree of pathophysiological heterogeneity, and a fluctuating clinical course. It has a strong genetic component and often coincides with other allergic disorders, including allergic rhinitis or asthma [24,25]. In a quite common version of the natural history of atopic dermatitis, loss of the integrity and structural function of skin epidermal barrier because of genetically mediated deficiency in the structural proteins, such as filaggrin (*FLG*) is followed by type-2-dominated immune responses characterized by increased expression of type-2 cytokines, such as IL-4, IL5, and IL-13 in the skin lesion, which is typically accompanied by an elevation in the allergen-specific and total serum immunoglobulin E (IgE) levels [26,25]. Other factors, such as skin microbiota also add to this complex interaction of genetic, immune, and environmental mechanisms ultimately leading to the development of atopic dermatitis in its various clinical forms [25,27]. There is increasing evidence that the epigenetic mechanisms including DNA methylation and histone modifications contribute to the pathophysiology of atopic dermatitis through gene-environment interactions [3,28].

Substantial differences in DNA methylation were observed between lesional epidermis obtained from atopic dermatitis patients and healthy control epidermis, which partially correlated with altered expression levels of genes primarily relevant for innate immune responses and for epidermal differentiation [29]. Moreover, discordant results were generated using DNA isolated from whole blood, T-cells, or B-cells for which no genome-wide significant differences in DNA methylation were detected

between atopic dermatitis cases and healthy control individuals, suggesting that blood is not a good proxy for the epidermis, at least for this type of the molecular analysis [29]. Significantly higher DNA methylation levels were, however, detected at the promoter region of the human β -defensin-1 (*HBD-1*) gene in atopic dermatitis lesional skin samples than in nonlesional atopic dermatitis skin or normal skin samples [30]. Another study demonstrated that the administration of trichostatin A (TSA), the HDAC inhibitor, was capable of reducing the hallmarks of the atopic dermatitis-like dermatitis induced in a mouse model. Moreover, TSA inhibited IL-4 but not IFN- γ production by CD4⁺ T-cells deriving from the lymph nodes. Taken together, those findings confirmed the involvement of histone acetylation in the pathobiology of atopic dermatitis and a potential of targeting histone acetylation as a candidate therapy for atopic dermatitis [31].

Other allergies

Epigenome-wide analysis performed using DNA extracted from whole blood demonstrated that allergic sensitization during adolescence was associated with DNA methylation patterns, partly in an age-specific manner [32^{¶¶}]. A comparative study conducted in peripheral blood CD4⁺ T-cells showed in turn that DNA methylation at the *IFNG* promoter was higher in allergic rhinitis than in healthy children, and this effect was indirectly related to the birth season [33]. Epigenome-wide studies demonstrated also the associations of blood (leukocyte) DNA methylome with food allergies, including cow's milk allergy [34–36]. Interestingly, a study in peanut-sensitized mice strongly suggested that the changes in the DNA methylation patterns at the important T-cell loci in the specific T-cell compartments, might explain the sustainability of antiallergic protection following epicutaneous immunotherapy [37^{¶¶}]. In addition, a comparative study conducted in PBMCs isolated from children with active cow's milk allergy and healthy controls showed a differential expression of several microRNAs [38[¶]]. A few further epigenetic studies relevant to asthma, allergic rhinitis, food allergy, and allergic sensitization are discussed in the next section.

POTENTIAL APPLICATIONS OF EPIGENETICS IN ALLERGIC DISORDERS

Diagnostics

Growing understanding of the contribution of epigenetic mechanisms to the development of allergies

yielded several recent studies investigating the potential diagnostic utility of the epigenetic patterns in those disorders (Supplementary Table 1, <http://links.lww.com/COAI/A18>). It was demonstrated that T-cell DNA methylation signatures are able to clearly separate allergic rhinitis patients from healthy controls, even outside the pollen season, and this separation was much better compared with when mRNA was used as a biomarker [39]. In addition, DNA methylation patterns assessed in PBMCs outperformed allergen-specific IgE and skin prick testing in predicting the oral food challenge outcomes in food-sensitized infants [40]. Similarly, in lymphocyte-enriched PBMCs obtained from patients with allergic rhinitis exposed to grass pollen in a controlled allergen challenge facility, predictive abilities for symptoms severity were demonstrated for DNA methylation at several loci, for example, *MUC4*. Furthermore, in nasal brushings obtained from an independent cohort exposed to birch pollen, changes in *MUC4* DNA methylation correlated with a decrease in peak nasal inspiratory flow [41[■]]. Another very recently conducted, rather large, study showed the nasal DNA methylome to be a sensitive biomarker of asthma, allergy, and airway inflammation [42[■]]. A very recently published study, nested within the prospective birth-cohort ALADDIN (Assessment of Lifestyle and Allergic Disease During INfancy), which consists of families with different lifestyles, anthroposophic, partly anthroposophic or conventional [43], analyzed the association between the histone acetylation in placenta and the risk of sensitization to food allergens or aeroallergens in early childhood, as assessed from 6 months up to 5 years of age [44[■]]. Associations of histone acetylation levels with risk of allergic sensitization in three genes were observed in the study subgroups. Lower risk of sensitization to food allergens was associated with higher H3 acetylation levels at the *IFNG* (boys) and *SH2B3* (children born in nonanthroposophic families), and higher H4 acetylation in *HDAC4* (girls). In addition, higher *HDAC4* H4 acetylation levels were also associated with a lower risk of sensitization to aeroallergens in female offspring. Those associations were in most of the cases mirrored by reasonable predictive abilities [44[■]]. Although several issues still need to be solved, including if the easily accessible tissues, such as peripheral blood are diagnostically valuable proxies of end-organs, such as lungs [3,5], the results of the recently published studies are encouraging.

Intervention

Several recent studies focused on the potential preventive or therapeutic applications of our

constantly increasing knowledge on the role of epigenetic mechanisms in allergic disorders (Supplementary Table 2, <http://links.lww.com/COAI/A18>). Treatment with JQ1/SGCBDO1 or I-BET762, BET bromodomain mimics, resulted in the inhibition of fetal calf serum/transforming growth factor β -induced proliferation of airway smooth muscle cells sampled from asthmatic patients and nonasthmatic individuals [45]. The application of JNJ-26481585, a broad-spectrum histone deacetylase inhibitor, restored the integrity of the nasal epithelium obtained from allergic rhinitis patients; moreover, JNJ-26481585 prevented the development of allergic airway inflammation or bronchial hyperreactivity in a mouse model [46[■]]. Prenatal diets or diet supplements known to exert protective effects against allergies were able to affect the histone acetylation profiles of important allergy-related immune regulatory genes in cord blood T-cells and placenta [47,48[■]]. In CD4⁺ T-cells obtained from cord blood of babies born from mothers treated during pregnancy with fish oil, a higher acetylation of histone H3 was observed at the promoter region of *PRKCZ*, the gene encoding T-cell protein kinase C (PKC) ζ [47], perhaps providing an explanation for the prenatal fish oil supplementation-related protection against allergic responses previously shown to be associated with and enhanced expression of PKC ζ in the cord blood T-cells [49,50]. Other genes histone acetylation of which was associated with in-utero fish oil supplementation constituted *IL13* and *TBX21* genes [47]. Another study analyzed the effect of the lifestyle and maternal diet, including olive oil and fish, on histone acetylation levels in placentas collected from the prospective birth cohort [48[■]], ALADDIN [43]. Interestingly, regular olive oil usage during pregnancy was in anthroposophic families associated with higher H3 acetylation at *FOXP3*, *IL10RA*, and *IL7R* gene promoters. Moreover, in female offspring, maternal fish consumption correlated with higher H4 acetylation at the *CD14* locus [48[■]]. In another animal study, in which mice were first pretreated with either processed (shop) or unprocessed (raw) cow's milk and then subjected to ovalbumin-based model of food allergy, histone H3 and H4 acetylation levels at the promoters of the T-cell genes were analyzed in splenocyte-derived CD4⁺ T-cells and the mesenteric lymph nodes [51[■]]. Opposite to shop milk, raw milk decreased the symptoms. Directly after milk exposure, there was a general immune stimulation reflected by increased histone acetylation at Th1, Th2, and regulatory T-cell (Treg) genes, which was more pronounced in raw vs. shop milk-treated mice. However, after allergy induction, this general immune stimulation resolved, and most importantly, histone acetylation of Th2 genes was

lower in raw milk-pretreated groups compared with processed milk-pretreated group, possibly explaining the protective effects of raw milk [51^{***}]. To summarize, epigenetic mechanisms, especially histone modifications, seem to represent a promising target for novel antiallergic therapies [10].

CONCLUSION

The contribution of the environmental factors to the development of asthma, allergic rhinitis, atopic dermatitis, food allergy, and other allergic diseases, mediated in huge part by the epigenetic mechanisms, has been well established. Also very recently, in the very last few years, a substantial progress has been achieved and, although further studies need to be conducted to dissect the epigenome of other allergic conditions and to better understand of the causes and molecular pathology of those diseases, the potential application of epigenetics in the diagnostics and therapy of allergies has clearly been shown. It does not only mean identification of the potential diagnostic or therapeutic targets but also direct usage of epigenetic marks in diagnostics assays and the application of epigenome-modifying tools in treatment, respectively.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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